Inheritance of intersex disorders

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Intersex disorders result from abnormalities of the sex chromosomes, gonads, internal and external genitalia, sex hormones and gender role. This article reviews the literature on intersex disorders, outlining the characteristics and mode of inheritance, if known, of each. For appropriate and effective management and counselling of patients and their families, physicians must have a good knowledge of the development of the genital tract and of the interaction between genetic sex and environmental influences.

Les troubles d'intersexualité résultent de perturbations des chromosomes sexuels, des gonades, des organes génitaux internes et externes, des hormones sexuelles ou des rôles sexuels. Cet article passe en revue la littérature relative aux troubles d'intersexualité, soulignant pour chacun les caractéristiques et le mode de transmission, lorsque celui-ci est connu. Pour traiter et orienter de façon adéquate et efficace ses patients ainsi que leur famille, le médecin doit posséder une bonne connaissance de l'embryologie des voies génitales et de l'interaction entre le sexe génétique et les facteurs environnementaux.

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Any discrepancy between the various components of human sexuality — sex chromosomes, gonads, internal or external genitals, sex hormones and gender role — may be regarded as an intersex disorder. It is well recognized that some intersex disorders can affect more than one member of a family. However, the modes of inheritance differ. Since this information is important in counselling, we review the present knowledge on intersex disorders.

Congenital adrenal hyperplasia

The adrenal gland synthesizes three main classes of hormones: mineralocorticoids, glucocorticoids and sex steroids. Congenital adrenal hyperplasia is due to an enzymatic defect in the production of cortisol and aldosterone. One of several enzymes — 21α-hydroxylase, 11β-hydroxylase and 3β-hydroxysteroid dehydrogenase — may be at fault,

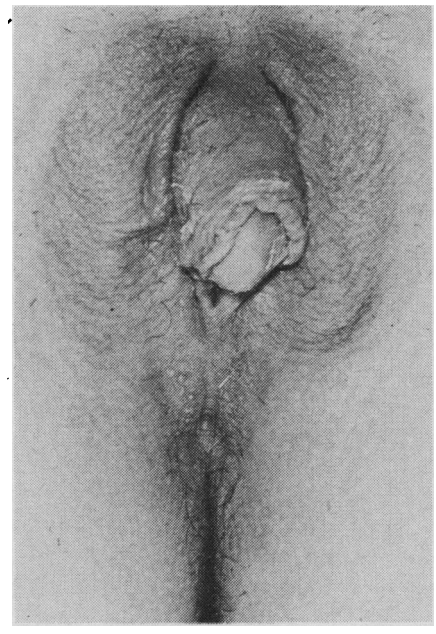

FIG. 1—External genitalia of genetic female with congenital adrenal hyperplasia.

21α-hydroxylase most commonly. In some intersex disorders the defect in cortisol production results in an increased production of androgens and masculinization of the genetically female fetus[1] (Fig. 1). In other intersex disorders deficiencies of 3β-hydroxysteroid dehydrogenase, 17α-hydroxylase or cholesterol desmolase decrease the production of testosterone, causing undervirilization in genetic males.

The distribution of affected individuals in families in which one or more members had congenital adrenal hyperplasia[2] has indicated the presence of a gene that manifests itself only in the homozygous state — that is, the gene is inherited in an autosomal recessive fashion.[2] Therefore, the risk that a woman with one affected child will have another affected child by the same husband is one in four. However, a woman with congenital adrenal hyperplasia will only have an affected child if her husband is also a carrier of the abnormal gene, the risk of which varies in a given population. The lowest such risk is estimated to be 1:128, in the United States,[3] and the highest to be 1:11, among Yupic Eskimos.[4] The risk of the carrier state of the salt-losing variety is estimated to be 1:82 in Canada.[3] Since a woman must be homozygous to be affected, if her husband is a carrier the risk of her offspring being affected is 1:2.

Recently a close genetic link has been demonstrated between the 21α-hydroxylase gene and the B locus of the HLA histocompatibility complex.[5,6] Such an association may permit prenatal diagnosis of an affected fetus through HLA typing of the amniotic fluid cells in pregnancies at risk.[7] But this method is indirect and is limited to women with an affected child who have informative HLA-B antigens. Furthermore, the method

has been reported to give false-positive results in some instances.[8] However, the few centres at which it is used are currently trying to assess its value and limitations.

Cortisol production is impaired in infants with congenital adrenal hyperplasia, and the serum levels of steroid precursors such as 17-OH-progesterone are increased in those who are not treated. The levels of steroid hormones in the amniotic fluid may reflect fetal steroidogenesis. Indeed, elevated levels of 17-OH-progesterone were found in the amniotic fluid of women whose infants had congenital adrenal hyperplasia.[9] Therefore, such measurements may be a useful addition to HLA typing in the prenatal diagnosis of this disorder.

Familial gonadal dysgenesis

Gonadal dysgenesis usually results from a chromosome defect that occurred during gametogenesis or early division of the zygote and is rarely familial. However, the condition may be found in phenotypic sisters in whom the karyotype is 46,XY or 46,XX (Fig. 2).

Familial gonadal dysgenesis with the 46,XY karyotype becomes apparent when karyotyping is done as part of the investigation of primary amenorrhea. Although the affected patient is a genetic male the phenotype is female since the streak gonads are unable to promote masculinization.[10] At least one type of this condition is transmitted by unaffected female carriers in X-linked recessive fashion.[11] However, since patients with this disorder are infertile and male-to-male transmission has not been documented, it is possible that a clinically indistinguishable disorder exists that is transmitted in autosomal dominant (male-limited) fashion.[12-14] With this form of inheritance the defective dominant gene is situated on an autosome, and its clinical expression is limited to the male, although the female is the carrier.

Familial gonadal dysgenesis with the karyotype 46,XX is not, strictly speaking, an intersex disorder. Its mode of inheritance is autosomal recessive;[15,16] therefore, consanguinity significantly increases the risk of its occurrence.

Familial gonadal dysgenesis is not associated with an abnormal karyotype or mosaicism and therefore is not amenable to prenatal diagnosis. Yet when the fetal karyotype is normal and therefore different from the one affecting the family (i.e., 46,XY in a family affected by XX gonadal dysgenesis) the infant is unlikely to be affected.

Androgen insensitivity

Genetic males with androgen insensitivity have normal testicular tissue that produces both androgens and müllerian inhibiting factor; however, the target tissues are resistant to androgen stimulation. Therefore, these patients have a 46,XY karyotype, testes, female external genitalia and no müllerian derivatives. At puberty, pubic and axillary hair are absent or scanty, but other female sexual features are well developed (Fig. 3). Menstruation does not occur.

Androgen insensitivity is trans-

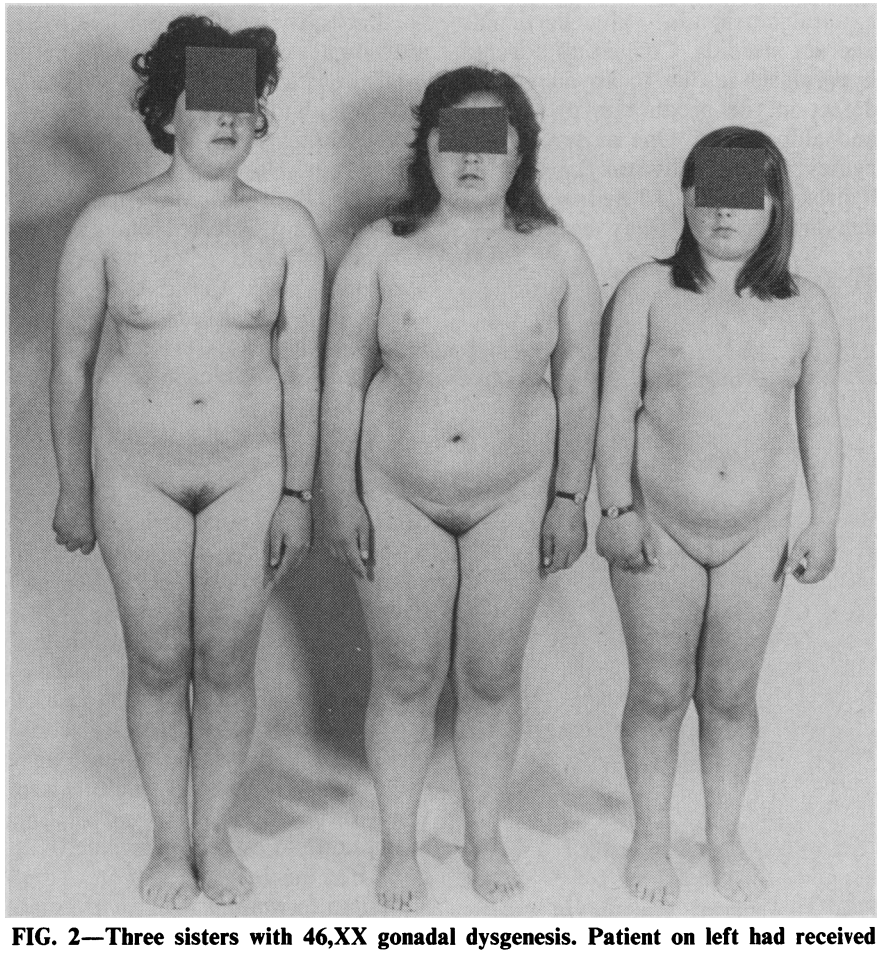

FIG. 2—Three sisters with 46,XX gonadal dysgenesis. Patient on left had received replacement estrogen therapy.

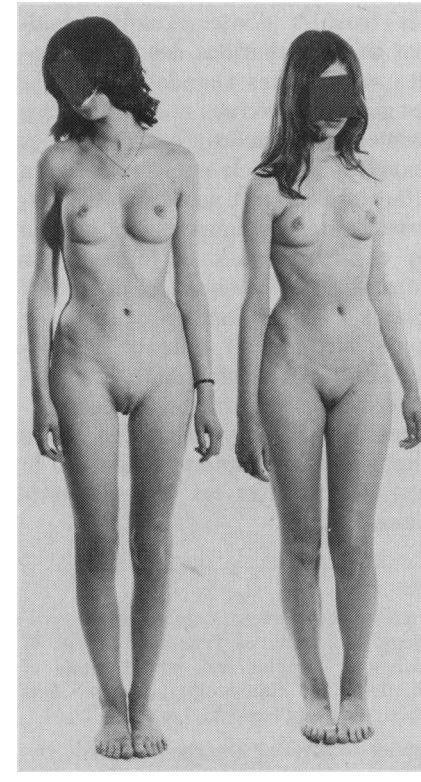

FIG. 3—"Sisters" with 46,XY karyotype and androgen insensitivity. (Reproduced, with permission, from reference 17.)

mitted from an unaffected female carrier to male offspring, as in 46,XY gonadal dysgenesis. However, since the affected males are infertile, there are again two possible modes of inheritance: X-linked recessive and sex-limited autosomal dominant.[18]

Although all patients with complete androgen insensitivity are similar phenotypically in that the basic defect is the inability of the end organ to respond to an androgen stimulus, the disorder can be divided into two types on the basis of the reason for the lack of response. Type 1 androgen insensitivity is characterized by a receptor deficiency — that is, androgens cannot be bound at the cellular level. Identification of the androgen receptors has provided the means to determine if the mode of inheritance of the defective gene is X-linked or autosomal dominant. If it were X-linked, the female carrier would be expected to have diminished androgen receptor activity. Since diminished activity has been documented, the mode of inheritance is indeed X-linked recessive.[19,20] In type 2 complete androgen insensitivity, which may be heterogeneous, androgens are bound by the target cells, but the use of the bound androgen is impaired.[19] The mode of inheritance, whether X-linked recessive or sex-limited autosomal dominant, has not yet been determined.

Some patients have incomplete androgen insensitivity. Their abnormal features include ambiguous genitalia with a variable degree of masculinization at birth (Fig. 4) and often poor virilization at puberty, although pubic and axillary hair develop. Since the patient's phenotype depends on the degree of androgen insensitivity, the clinical presentations of this disorder differ greatly. Reifenstein's syndrome[21] should probably be considered a variant of incomplete androgen insensitivity;[22] however, some still consider it a separate entity.[18]

Incomplete androgen insensitivity, including Reifenstein's syndrome, is probably inherited as an X-linked recessive disorder, although it may be inherited as a sex-limited autosomal dominant disorder.[23]

Prenatal diagnosis is not feasible at present. However, since the disorder is limited to genetic males, the presence of a female karyotype in the fetus would guarantee an unaffected genetic female.

Deficiency of 5α-reductase

This condition results from the faulty conversion of testosterone to dihydrotestosterone as a result of 5α-reductase deficiency. The patients have a 46,XY karyotype, bilateral testes at various locations and male internal genitalia. The external genitalia are ambiguous and poorly developed (Fig. 5). At puberty virilization occurs, with phallic enlargement and the development of a male hair distribution and a male habitus; the breasts do not develop. Some patients who have been reared as girls later assume a male role.[25,26]

A deficiency of 5α-reductase is inherited in an autosomal recessive fashion. It has often been associated with consanguinity[27] and has been found to be most common in remote areas where people are inbred.[24,27]

Currently prenatal diagnosis of 5α-reductase deficiency is impossible. However, as with androgen insensitivity, the disorder affects only genetic males. Theoretically the amniotic cells could be cultured and the rate of conversion of testosterone to dihydrotestosterone measured. This technique has never been attempted however. It has been suggested that the conversion of testosterone to dihydrotestosterone by fibroblasts is similar to that by the urogenital sinus.[28] In some cases it is possible, at least theoretically, to obtain fetal cells with a fetoscope and measure the activity of 5α-reductase.

Persistent müllerian duct syndrome

The persistent müllerian duct syndrome, which affects males, results

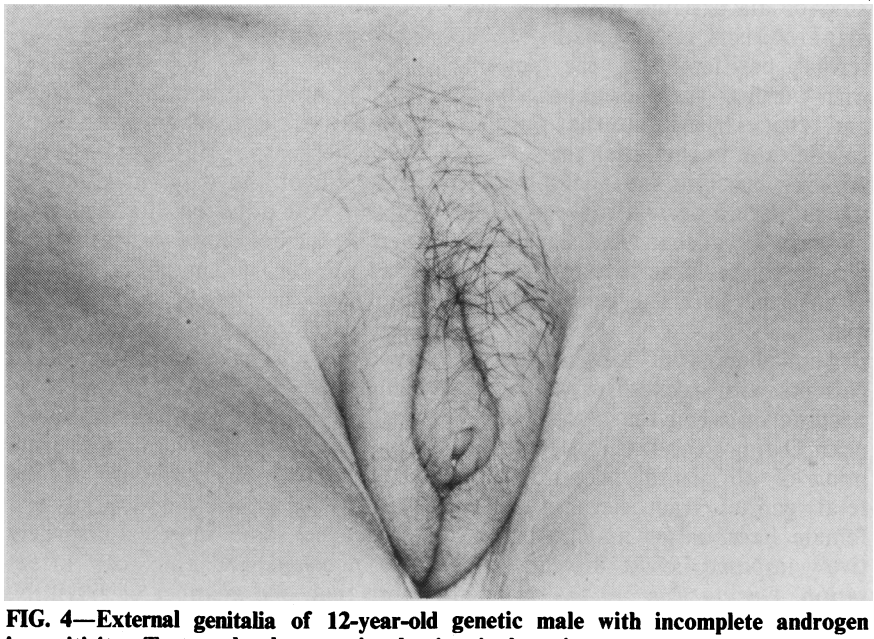

FIG. 4—External genitalia of 12-year-old genetic male with incomplete androgen insensitivity. Testes clearly seen in the inguinal region.

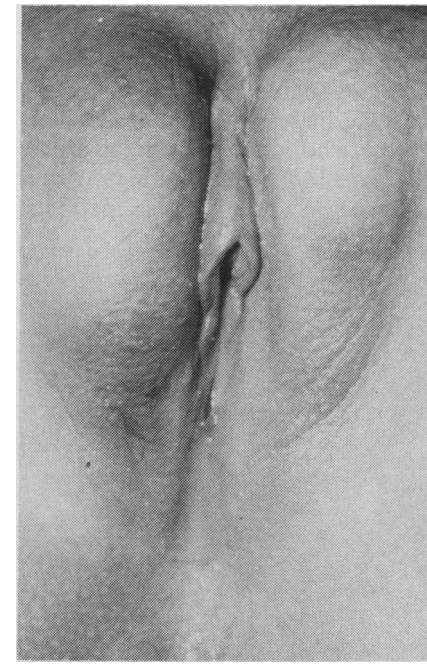

FIG. 5—External genitalia of 10-year-old genetic male with 5α-reductase deficiency. Testes clearly visible in "labia", although enlargement of phallus is minimal. (Reproduced, with permission, from reference 24.)

from a defect in the production of or a lack of response to müllerian inhibiting factor. As a result, fallopian tubes, uterus and upper vagina are found in males who are otherwise normal or nearly normal.

This disorder usually presents as a simple inguinal hernia in which a small uterus and fallopian tubes are found; cryptorchidism is sometimes associated. The condition is inherited in X-linked recessive or sex-limited autosomal dominant fashion.[29]

Since the syndrome affects only genetic males, the presence of a 46,XX karyotype in the fetus guarantees an unaffected female infant.

Males with a 46,XX karyotype

When a Y chromosome is absent, the indifferent embryonic gonad becomes an ovary and the fetus develops as female even if no germ cells are present. When a Y chromosome is present, testes develop and produce testosterone, which in turn induces masculinization of the fetus. However, there are a few individuals whose sexual development appears to be male even though the chromosomal complement — 46,XX — is female (Fig. 6). These patients have small testes and some signs of androgen deficiency, but the external genitalia are definitely male, so there is no question as to whether the child should be reared as male.[30] In some males with the 46,XX karyotype who were not studied by de la Chapelle,[30] genital ambiguity was observed.[31,32] In all these patients, virilization at puberty is impaired; in addition, the growth of body and facial hair is decreased, and its distribution may be similar to that in females. Gynecomastia is noted in about one third of the patients.[30] Familial cases have been reported by several investigators.[33-36]

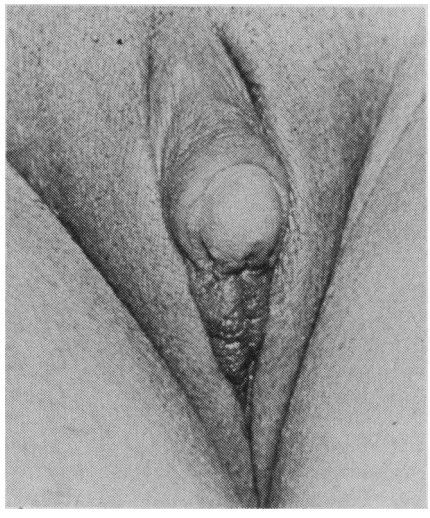

FIG. 6—External genitalia of 46,XX adolescent with karyotype and familial true hermaphroditism.

Testicular differentiation is determined by the H-Y antigen, a cell surface component that is usually present only when a Y chromosome exists.[37,38] It has been postulated that in males with the XX karyotype a translocation of the H-Y locus to an autosome or an X chromosome provides the developing embryo with H-Y surface antigen, which promotes testicular differentiation;[18] hence, the disorder is inherited as a dominant trait. However, from the results of an extensive study of a large pedigree, it seems possible that at least in some of these "sex reversal" patients the inheritance is autosomal recessive.[36]

Disorders for which the mode of inheritance is unknown

Two other conditions — true hermaphroditism and agonadism — may be familial, but their mode of inheritance is not yet known. Only a few pedigrees of familial cases of true hermaphroditism have been reported in the literature[38-42] or to us (D.B. Grant: personal communication, 1982); however, these patients form a unique group. While only 26% of all patients with true hermaphroditism have gonads in the scrotal position,[43] all the patients with familial true hermaphroditism had testicular tissue in that position. In addition, in the latter there was a 46,XX chromosome complement, the müllerian derivatives were rudimentary or absent, and except for the pedigree described to us by Grant, the external genitalia were male.

The phenotypic presentation of patients with agonadism varies, depending on when the gonads disappear. Owing to an intrinsic programming of all genital primordia, the fetal genital tract develops along female lines unless maleness is actively imposed before 8 weeks' gestation. During this critical stage of embryonic development the fetus has two pairs of internal genital ducts, and the müllerian ducts are sensitive to müllerian inhibiting factor. After 8 weeks, exposure to fetal testes and thus to müllerian inhibiting factor does not prevent normal development of the müllerian ducts.

The wolffian ducts become androgen-dependent when renal function has been taken over by the definitive kidney; the ducts disappear at this time in the absence of androgens. If androgens are present the ducts become stable and no longer require androgens for maintenance, although androgen stimulation is needed for subsequent differentiation. The external genitalia also need androgenic stimulation to develop along male lines. The degree of their masculinization depends on the amount of androgens and on the timing and duration of exposure. When testes involute following a period of production of müllerian inhibiting factor and androgens, the clinical findings depend on the amount of previous testicular activity and the timing of involution in relation to the critical period of development of the internal and external genitalia.

Patients with agonadism have a slightly enlarged phallus, underdeveloped and partially fused labia, and a urogenital sinus. Only remnants of internal genitalia exist, and gonadal tissue is absent. The condition is rare, and although it has been reported in siblings[44] its mode of transmission is unknown.[44,45]

Management

A newborn infant with genital ambiguity represents an acute medical emergency. With appropriate management the child may have a happy, well adjusted life and may even be fertile. However, with inappropriate or no management the child may be considered a "freak" and therefore suffer loneliness and frustration. The sex of the child should be "assigned" as soon as possible. Regardless of the complexity of doing so, the choice will often be the main determinant of the outcome for the child and family.

Because some intersex disorders are inherited and thus can affect more than one member of a family, the physician must have a rational approach to a family's questions on

ambiguous genitalia. Knowledge of the embryologic development of the genital tract, the interaction between genetic sex and environmental influences, and the mode of inheritance of the disorder will help the physician diagnose the problem, identify other affected family members and predict the risk that the mother will have another affected infant should she become pregnant.

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